The expression of the major histocompatibility complex (MHC) class II gene family is developmentally regulated and, in general, in a coordinate manner. In this study, we show that the expression of the entire repertoire of human class II genes, otherwise transcriptionally silent in the bare lymphocyte syndrome-derived BLS1 cell line, can be rescued by somatic cell hybridization with normal mouse spleen cells. The analysis of the interspecies cell hybrids revealed a particularly important and unprecedented aspect. A return to the BLS1-like, human MHC class II-negative phenotype due to segregation of mouse chromosomes was accompanied in certain hybrids by loss of IE, but not IA cell surface antigen expression. At the molecular level, this was the result of lack of Eα-specific mRNA in the presence of Eβ-, Aα- and Aβ-specific mRNA. Thus, the mouse *trans*-acting function operating across species barriers and able to complement the defect of human BLS1 cells diverged in mice to control *Ea*, but not *Eb, Aa* and *Ab* gene expression. These findings suggest that evolutionary pressure has maintained the expression of the MHC class II multigene family under the control of quite distinct species-specific transcriptional mechanisms.